REMARKS

Reconsideration of the above-identified application in view of the amendments above and the remarks following is respectfully requested.

Claims 1-119 are in this case. Claims 5-9 and 29-119 were withdrawn under a restriction requirement as drawn to a non-elected invention. Claims 1-4 and 10-28 have been rejected. Claims 16-25 and 27-28 have now been canceled. Claims 1-3, 10, 12-15 and 26 have now been amended. New claims 120-127 have now been added.

35 U.S.C. § 112, First Paragraph, Rejections

The Examiner has rejected claims 27 and 28 under 35 U.S.C. § 112, first paragraph for lacking enablement for administering an inhibitor of a glutamate synthesizing enzyme.

Claims 27 and 28 have now been canceled to thereby render moot Examiner's rejection.

35 U.S.C. § 112, Second Paragraph, Rejections

The Examiner has rejected claims 3, 4, 12-14, 16, 17-25 under 35 U.S.C. 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

The Examiner states that the use of the phrase "an enzyme incapable of converting modified glutamate into glutamate" is confusing.

Claims 16-25 have now been canceled. Claims 2, 12-14 and 17-25 have now been amended such that the enzyme is defined as being an artificially modified (as opposed to the naturally occurring enzyme of claim 2) glutamate modifying enzyme which is incapable (such as due to directed in vitro evolution or mutagenesis, described at pages 20-21 of the specification) of mediating the reverse reaction of naturally occurring glutamate modifying enzymes; essentially, the conversion of modified glutamate (2-keto-glutarate) back to glutamate. Such enzymes are expected to increase the brain to blood efflux.

In addition claims 12-14 were amended to replace the phrase "said modified glutamate" with "modified glutamate", thereby rendering moot Examiner's rejection.

The Examiner further states that the phrase" being selected incapable of..." is confusing. The term "selected" has now been removed from claims 12-14, thereby rendering moot Examiner's rejection.

The Examiner states that it is unclear if "glutamate modifying enzyme" and "glutamate converting enzyme" is the same enzyme since GOT is defined by both. In order to clarify, Applicant has amended claims 12-14, to comprise a uniform language of "glutamate modifying enzyme".

In view of the above amendments Applicant believes to have overcome the rejections under 35 U.S.C 112 second paragraph.

35 USC § 102

The Examiner has rejected claims 1, 2, 10, 11 and 26 under 35 USC 102(b) as being anticipated by WO 99/21565.

The Examiner states that WO 99/21565 discloses a method of treating individuals with disorders related to impaired mitochondrial and cerebral function. Such disorders are contributed by glutamate-induced neuronal death.

Specifically, the Examiner states that WO '565 teaches treating such disorders by administering a Kreb's cycle intermediate (e.g., oxaloacetate) similarly to the claimed invention. The Examiner's rejection is respectfully traversed. Claim 1 has now been amended. New claims 122-127 have now been added.

The present invention relates to a novel finding by the present inventor whereby high and deleterious extracellular brain glutamate can be eliminated by reducing blood glutamate levels and consequently increasing the brain to blood glutamate efflux.

This finding enabled to generate highly efficient therapeutic compositions which can be utilized to treat clinical conditions characterized by elevated extracellular brain glutamate levels without the need to cross the blood brain barrier. Such compositions may include glutamate modifying enzymes (e.g., GOT and GPT) and co-factors (also termed co-substrates) of same (e.g., oxaloacetate and pyruvate) which enhance the metabolism of blood glutamate to 2-keto-glutarate, thereby reducing the levels of blood glutamate and enhancing the brain to blood glutamate

efflux. Other agents which can mediate such efflux are shown in the Examples section (see for example, Example 4 of the present specification).

As shown in the Examples section of the instant application, administration of any of these agents or combination of same caused rapid decrease of blood glutamate levels which in turn caused a decrease in extracellular brain glutamate substantiating the use of the agents of the present invention for treating medical conditions of the CNS in which rapid reduction in the high and deleterious extracellular brain glutamate is required.

In sharp contrast to the present invention, the art of WO 99/21565 suggests the treatment of metabolic disorders associated with impaired mitochondrial function by the combined administration of high doses of a Kreb's cycle intermediate (e.g., oxaloacetate) and sugar each of which should penetrate the BBB. The protocol attempted in WO 99/21565 is directed at altering intracellular glutamate levels (as evidenced by measuring glutamate in whole brain homogenate which includes broken cells) which is in sharp contrast to the present invention in which reduction of extracellular glutamate is sought. In addition WO 99/21565 is silent with respect to the administration of glutamate modifying enzymes for the treatment of medical conditions of the CNS.

In order to distinct the claimed invention from WO 99/21565, Applicant has elected to amend claim 1 and add new independent claim 122 and claims dependent therefrom, which relate to the administration of a glutamate modifying enzyme and optionally a co-factor of same.

In addition Applicant has added new claim 125 which excludes (by the use of a "proviso" language) the administration of a pharmaceutical composition which comprises sugar when the co-factor is oxaloacetate. This is in sharp contrast to WO 99/21565 which requires the use of both oxaloacetate and sugar for achieving a therapeutic effect. Support for this claim language can be found in page 25 line 4 of the instant specification.

Thus, WO 99/21565 does not teach all of the limitations of amended claim 1, and new claims 122-127, and therefore do not, and cannot anticipate, alone or in combination with other references, the methods of the claimed invention. Applicant therefore requests withdrawal of the rejection.

The Examiner further rejected claims 1, 14, 15 and 26 under 35 USC 102(b) as being anticipated by Geng et al. (J. of Neurochemistry vol. 68, no. 6, 1997).

The Examiner states that Geng et al. teach the administration of pyridoxal phosphate to epileptic patients, thereby anticipating the claimed subject matter.

As mentioned hereinabove, the essence of the present invention is in the novel discovery of the present inventors whereby extracellular brain glutamate may be reduced by enhancing the brain to blood glutamate efflux and negating the need for administering the drug directly to the brain or formulate it such that it passes the BBB.

In Geng et al. the authors failed to understand the aforementioned mechanism and therefore resorted to tissue culture (in vitro) assays on cells (see page 2500 last paragraph and page 2501 first paragraph). Hence it is Applicant strong opinion that Geng et al. do not teach, suggest or mention the reduction of blood glutamate since it describes a tissue culture work and presents obstacles associated with using in vivo models i.e., penetration through the BBB *("It is difficult to study hypoglycemia-induced neuronal injury in vivo..."* Page 2501, right column, first paragraph).

Therefore Geng et al. do not, and cannot anticipate, alone or in combination with other references, the methods of the claimed invention. Applicant therefore requests withdrawal of the rejection.

In view of the above amendments and remarks it is respectfully submitted that claims 1-4, 10-15, 26 and 120-127 are now in condition for allowance. Prompt notice of allowance is respectfully and earnestly solicited.

Respectfully submitted,

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